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(54) Title: RECEPTOR SELECTIVE CANNABIMIMETIC AMINOALKYLINDOLES

(57) Abstract: Disclosed are cannabimimetic aminoalkylindole compounds and methos for their manufacture. The disclosed compounds are surprisingly potent and selective cannabinoinds. Also disclosed are methods of using the disclosed compounds, including use of the disclosed compounds to stimulate a cannabinoid receptor, to provide a physiological effect in an animal or individual and to treat a condition in an animal or individual.

# RECEPTOR SELECTIVE CANNABIMIMETIC AMINOALKYLINDOLES

## Field of the Invention

The present invention relates generally to indole compounds exhibiting cannabimimetic activity. The present invention is more particularly concerned with new and improved aminoalkylindole compounds exhibiting high binding affinity for at least one cannabinoid receptor and/or high selectivity for one cannabinoid receptor, pharmaceutical preparations employing these compounds and methods of administering therapeutically effective amounts of these compounds to provide a physiological effect.

## Background of the Invention

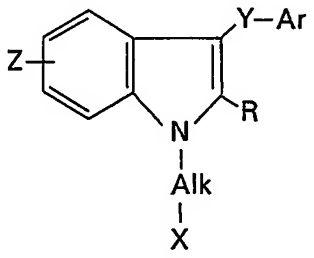
Classical cannabinoids such as the marijuana derived cannabinoid $\Delta^9$-tetrahydrocannabinol, ($\Delta^9$-THC) produce their pharmacological effects through interaction with specific cannabinoid receptors in the body. So far, two cannabinoid receptors have been characterized: CB1, a central receptor found in the mammalian brain and peripheral tissues and CB2, a peripheral receptor found only in the peripheral tissues. Compounds that are agonists or antagonists for one or both of these receptors have been shown to provide a variety of pharmacological effects.

There is considerable interest in developing cannabimimetic compounds possessing high affinity for one of the CB1 or CB2 receptors. Such compounds may offer a rational therapeutic approach to a variety of disease conditions. One class of cannabimimetic compound encompasses indole derivatives such as the well-known aminoalkylindoles represented by WIN 55212-2 {(R)-(+)-[2,3-dihydro-5-methyl-3-[(4-morpholinyl)methyl]-pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl](1-naphthalenyl)methanone}. Aminoalkylindoles of this type typically have a carbon linked alkylheterocyclic substituent at the indole-1 position, which is believed to be important for their cannabimimetic activities. These known materials are not selective for preferential activation of one of the CB1 or CB2 receptors.

**Summary of the Invention**

It has now been found that certain aminoalkylindoles possess surprising cannabimimetic properties, including selectivity for the CB1 or CB2 cannabinoid receptor. Broadly, in one aspect of the invention the novel cannabimimetic compounds can be represented by the structural formula I below, physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof.

structural formula 1




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two

substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $SO_2NR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

In one preferred aspect of the invention the novel compounds can be represented by structural formula I above, wherein:

wherein:

Z comprises hydrogen;

Alk comprises a $C_{1-2}$alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

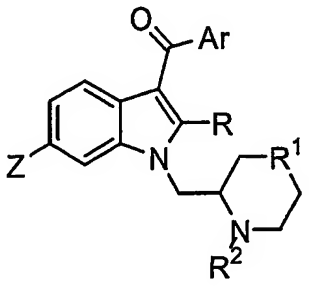
R comprises hydrogen;

Y comprises carbonyl; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $SO_2NR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

In another preferred aspect of the invention the novel compounds can be represented by structural formula II below,

structural formula II




wherein:

Z comprises hydrogen;

R comprises hydrogen;

$R^1$ comprises N, O, S or $CH_2$;

$R^2$ comprises H, alkyl, $CF_3$, $CH_2C{\equiv}CH$, $CH_2CH=CH_2$ or $CH_2Ph$; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $SO_2NR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

Unless otherwise specifically defined, "alkyl" refers to a linear, branched or cyclic alkyl group having from 1 to about 9 carbon atoms including, for example, methyl, ethyl, propyl, butyl, hexyl, octyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, cyclooctyl, vinyl and allyl. The alkyl group can be saturated or unsaturated and substituted or unsubstituted. Unless otherwise specifically defined, "lower-alcohol" refers to the general formula alkyl-OH. Unless otherwise specifically defined, "alkoxy" refers to the general formula -O-alkyl. Unless

otherwise specifically defined, "alkylmercapto" refers to the general formula -S-alkyl. Unless otherwise specifically defined, "alkylamino" refers to the general formula -(NH)-alkyl. Unless otherwise specifically defined, "di-alkylamino" refers to the general formula -N-(alkyl)$_2$. Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure, substituted or unsubstituted, that includes only carbon as ring atoms. Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure, substituted or unsubstituted, that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, pyridine, furan, quinoline, and their derivatives. Unless otherwise specifically defined, a carbocyclic ring is a saturated ring structure, substituted or unsubstituted, that includes only carbon as ring atoms, for example, cyclohexane. Unless otherwise specifically defined, a heterocyclic ring is a saturated ring structure, substituted or unsubstituted, that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, piperidine, morpholine, piperazine, and their derivatives. Unless otherwise specifically defined, an aliphatic bicyclic ring is a polycyclic structure, substituted or unsubstituted, having about 6 to about 12 ring atoms that includes only carbon as ring atoms, for example bicyclohexane and bicyclodecane. Unless otherwise specifically defined, a heterobicyclic ring is a polycyclic structure, substituted or unsubstituted, having about 6 to about 12 ring atoms that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example tropane.

Substituent groups useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Unless otherwise specifically defined, substituent groups that do not significantly diminish the biological activity of the inventive compound include, for example, alkyl, substituted alkyl, phenyl, substituted phenyl, OH, $NH_2$, alkoxy, halogen, $CF_3$, CN, NCS, azido, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $SO_2NR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$, sulfonamide, or lower alcohol.

Some of the inventive cannabinoid compounds exhibit high affinity for the CB1 and/or CB2 cannabinoid receptor. More specifically, some of the inventive analogs showed similar or higher receptor binding affinity than the well-known indole cannabinoid WIN 55212-2. Thus, another aspect of the invention is use of at least one of the inventive compounds to interact with a cannabinoid receptor.

Further, some of the inventive cannabinoid compounds show a surprisingly higher selectivity for one of the CB1 or CB2 cannabinoid receptors. These inventive selective compounds are able to interact with one cannabinoid receptor, for example the CB2 receptor, without affecting the CB1 cannabinoid receptor to the same degree. More specifically, some of these compounds show not only comparable cannabimimetic activity with the compound WIN 55212-2, but also a surprisingly higher selectivity for one of the CB1 or CB2 receptors. Therefore, still another aspect of the invention is use of at least one of the inventive compounds to preferentially interact with one cannabinoid receptor.

Some of the inventive cannabinoid compounds can act as high affinity modulators for the CB2 cannabinoid receptor. The inventive cannabinoid compounds therefore are potential therapeutic agents through the modulation of a cannabinoid receptor.

Some of the novel cannabinoid compounds described herein may be agonists for at least one of the cannabinoid receptors. The inventive cannabinoid agonists interact with the at least one cannabinoid receptor binding site to initiate a physiological or a pharmacological response characteristic of that receptor. Therefore, a further aspect of the invention is use of at least one of the inventive compounds to initiate an agonistic response from a cannabinoid receptor.

Some of the novel compounds described herein may be cannabinoid receptor antagonists. The inventive cannabinoid antagonists interact with the CB1 and/or CB2 cannabinoid receptor binding site to block other ligands from the receptor binding site without initiating a physiological or a pharmacological response characteristic of that receptor. Thus, cannabinoid antagonists typically oppose the cannabinoid receptor site response characteristics initiated by cannabinoid agonists. Therefore, a further aspect of the invention is use of at least one of the inventive

compounds to oppose initiation of an agonistic response from a cannabinoid receptor.

The inventive cannabinoid compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response in individuals and/or animals. Thus, another aspect of the invention is the administration of a therapeutically effective amount of at least one of the inventive cannabimimetic compounds, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological response.

Additionally, some of the halogen containing analogs, for example those analogs comprising iodide and fluoride, are potential radioactive probes for imaging *in vivo* the distribution of cannabinoid receptors.

A better understanding of the invention will be obtained from the following detailed description of the article and the desired features, properties, characteristics, and the relation of the elements as well as the process steps, one with respect to each of the others, as set forth and exemplified in the description and illustrative embodiments.

**Description of a Preferred Embodiment**

As used herein, a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a discernible increase or decrease in stimulation of cannabinoid receptors. Such discernible increase or decrease in stimulation of cannabinoid receptors can provide a physiological effect in the individual or animal.

Physiological effects that result from CB1 cannabinoid receptor interaction with agonist compounds include relief of pain, peripheral pain, neuropathic pain, glaucoma, epilepsy and nausea such as associated with cancer chemotherapy; appetite enhancement; selective killing of glioma and breast cancer cells; alleviation of the symptoms of neurodegenerative diseases including Multiple Sclerosis, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, reduction of

fertility; prevention or reduction of diseases associated with motor function such as Tourette's syndrome; neuroprotection; suppression of memory and peripheral vasodilation. Physiological effects that result from CB1 cannabinoid receptor interaction with antagonist compounds include appetite suppression; memory enhancement; beneficial effects in mental disorders such as schizophrenia and depression; and beneficial effects in endotoxic and hypotensive shock. Physiological effects that result from CB2 cannabinoid receptor interaction with agonist compounds include relief of pain, peripheral pain, neuropathic pain, glaucoma, epilepsy and nausea such as associated with cancer chemotherapy; selective killing of glioma and breast cancer cells; alleviation of the symptoms of neurodegenerative diseases including Multiple Sclerosis, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, reduction of fertility; prevention or reduction of diseases associated with motor function such as Tourette's syndrome; prevention or reduction of inflammation; neuroprotection; and suppression of the immune system. Physiological effects that result from CB2 cannabinoid receptor interaction with antagonist compounds include enhancement of the immune system and peripheral vasoconstriction. Typically a "therapeutically effective amount" of the novel compounds ranges from about 10 mg/day to about 1,000 mg/day.

As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

The compound of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to, capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular or subcutaneous administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically to acceptable vehicles may include, for

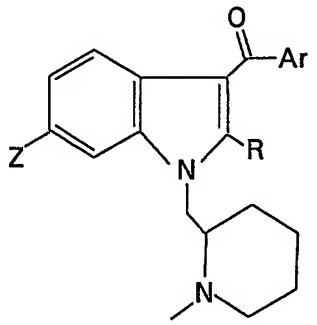
example, saline, sterile water, Ringer's solution, and isotonic sodium chloride solutions. The specific dosage level of compound will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

The prepared cannabimimetic indole derivatives can generally be described with reference to exemplary structural formulas 1 and 2 below.

The inventive compounds of exemplary structural formula 1 include both racemics and two enantiomers and are listed in TABLE 1.

exemplary structural formula 1




It should be noted that alk-X for all of the materials of TABLE 1 was 1-(N-methyl-2-piperidinyl)methyl.

**TABLE 1**

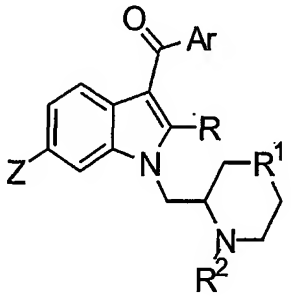
| | | | | $K_i$ nM | |
|---|---|---|---|---|---|
| analog | Z | R | Ar | CB1 | CB2 |
| | | | | | |
| 2-7(R,S) | H | H | 2-iodo-5-nitrophenyl | 403 | 5.7 |
| 2-7(R) | H | H | 2-iodo-5-nitrophenyl | 285 | 0.53 |
| 2-7(S) | H | H | 2-iodo-5-nitrophenyl | 906 | 9.5 |

| TABLE 1 | | | | | |
|---|---|---|---|---|---|
| | | | | $K_i$ nM | |
| analog | Z | R | Ar | CB1 | CB2 |
| | | | | | |
| 2-7(R,S) human | H | H | 2-iodo-5-nitrophenyl | | 1.6 |
| 2-24(R) | H | H | 2-iodophenyl | 1.8 | 2.1 |
| 2-24(S) | H | H | 2-iodophenyl | 561 | 583 |

Surprisingly, and as exemplified by compounds 2-7 and 2-24, in all cases the + configuration (R configuration) has a higher selectivity for the CB2 receptor and a higher affinity for the CB2 receptor.

Compound 2-7 was tested for binding affinity to human CB2 receptors using the below described procedure with human tissue samples. That compound was found to be a surprisingly potent cannabinoid.

exemplary structural formula 2



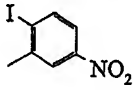

| TABLE 2 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | Ki nM | |
| analog | Z | R | $R^1$ | $R^2$ | Ar | CB1 | CB2 |
| | | | | | | | |
| 2-25 | H | H | O | $CH_2Ph$ |  | 1217 | 1800 |
| 2-26 | H | H | O | $CH_2Ph$ |  | 4212 | 1431 |

TABLE 2

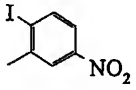
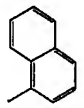
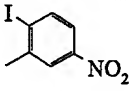
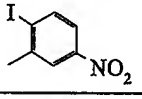
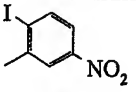
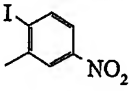
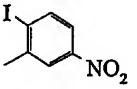
| | | | | | | Ki nM | |
|---|---|---|---|---|---|---|---|
| analog | Z | R | $R^1$ | $R^2$ | Ar | CB1 | CB2 |
| | | | | | | | |
| 2-27 | H | H | O | $CH_2Ph$ |  | 2383 | 927.5 |
| 2-28 | H | H | O | $CH_3$ |  | 27.93 | 226:3 |
| 2-29 | H | H | O | $CH_3$ |  | 848.1 | 48.45 |
| 2-30 | H | H | O | $CH_3$ |  | 464.3 | 153.5 |
| 2-31 | H | H | O | $CH_3$ |  | 5.696 | 26.56 |
| 2-32(R,S) | H | H | $CH_2$ | $CH_3$ |  | 239.4 (R,S) | 3.411 (R,S) |
| 2-32(R) | H | H | $CH_2$ | $CH_3$ |  | 139.7 (R) | 1.416 (R) |
| 2-32(S) | H | H | $CH_2$ | $CH_3$ |  | 2029 (S) | 160.5 (S) |
| 2-32(R,S) human | H | H | $CH_2$ | $CH_3$ |  | | 13.60 (R,S), Human |
| 2-32(R) human | H | H | $CH_2$ | $CH_3$ |  | | 6.688 (R), Human |
| 2-33 | H | H | $CH_2$ | $CH_3$ | 1-Adamantyl | 11.93 | 4.804 |
| 2-33 human | H | H | $CH_2$ | $CH_3$ | 1-Adamantyl | | 2.321 Human |
| 2-34(R,S) | H | H | $CH_2$ | $CH_3$ |  | 2.889 (R,S) | 3.345 (R,S) |
| 2-34(R) | H | H | $CH_2$ | $CH_3$ |  | 1.573 (R) | 1.558 (R) |
| 2-34(S) | H | H | $CH_2$ | $CH_3$ |  | 14.17 (S) | 6.789 (S) |

TABLE 2

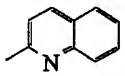
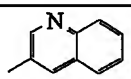
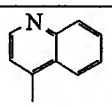
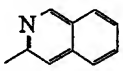
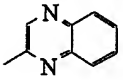
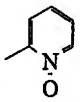
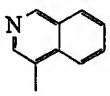
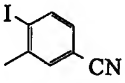
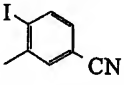
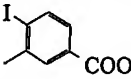
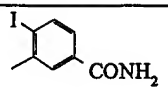
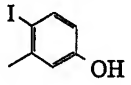
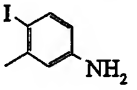
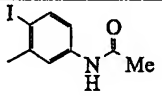
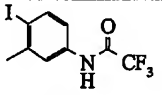
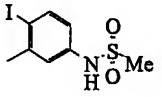
| | | | | | | Ki nM | |
|---|---|---|---|---|---|---|---|
| analog | Z | R | $R^1$ | $R^2$ | Ar | CB1 | CB2 |
| 2-34(R,S) human | H | H | $CH_2$ | $CH_3$ |  | | 2.488 Human |
| 2-35 | H | H | $CH_2$ | $CH_3$ |  | 14.36 | 20.93 |
| 2-36 | H | H | $CH_2$ | $CH_3$ |  | 133.1 | 8.532 |
| 2-37 | H | H | $CH_2$ | $CH_3$ |  | 3541 | 836.6 |
| 2-38 | H | H | $CH_2$ | $CH_3$ |  | 719.3 | 747.5 |
| 2-39 | H | H | $CH_2$ | $CH_3$ |  | 41.44 | 19.53 |
| 2-40 | H | H | $CH_2$ | $CH_3$ |  | 28.65 | 14.54 |
| 2-41 | H | H | $CH_2$ | $CH_3$ |  | 157.8 | 159.7 |
| 2-42 | H | H | $CH_2$ | $CH_3$ |  | 421.4 | 147.2 |
| 2-43 | H | H | $CH_2$ | $CH_3$ |  | 8816 | 1858 |
| 2-44 | H | H | $CH_2$ | $CH_3$ |  | 16.94 | 7.037 |
| 2-45 | H | H | $CH_2$ | $CH_3$ |  | 418.5 | 15.82 |
| 2-46 | H | H | $CH_2$ | $CH_3$ |  Hydrochloride | 338.7 | 15.41 |
| 2-47 | H | H | $CH_2$ | $CH_3$ |  Hydrochloride | 240.2 | 18.76 |

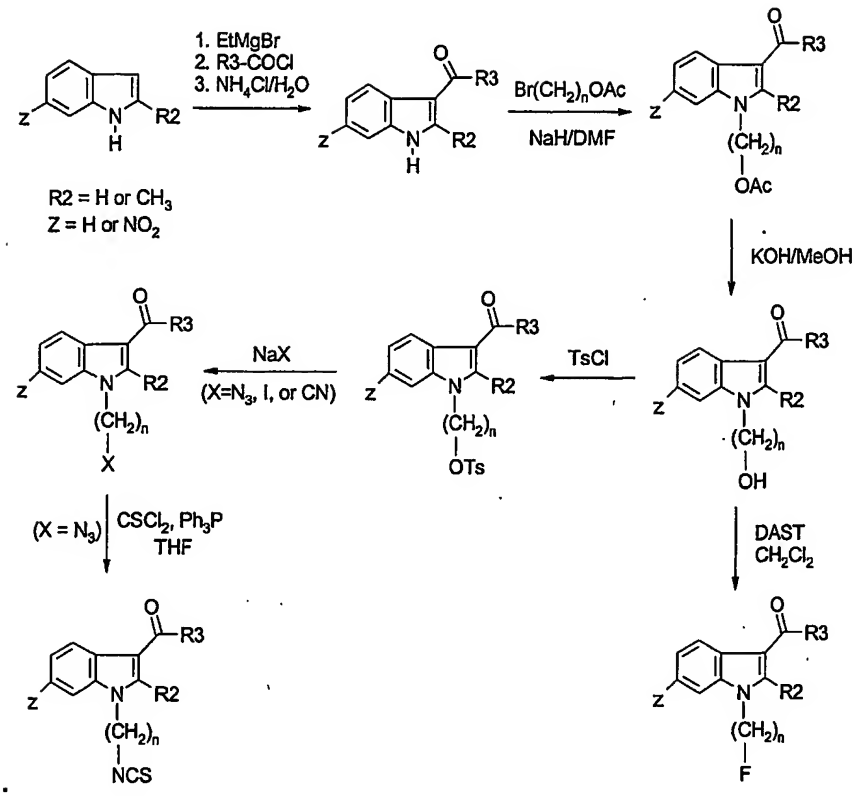
TABLE 2

| | | | | | | Ki nM | |
|---|---|---|---|---|---|---|---|
| analog | Z | R | $R^1$ | $R^2$ | Ar | CB1 | CB2 |
| | | | | | | | |
| 2-48 | H | H | $CH_2$ | $CH_3$ |  | 390.0 | 47.17 |
| 2-49 | H | H | $CH_2$ | $CH_3$ |  | 29.07 | 18.63 |
| 2-50 | H | H | $CH_2$ | $CH_3$ |  | | |
| 2-51 | H | H | $CH_2$ | $CH_3$ |  | | |
| 2-52 | H | H | $CH_2$ | $CH_3$ |  | | |
| 2-53 | H | H | $CH_2$ | $CH_3$ |  | | |

Preparation of compounds:

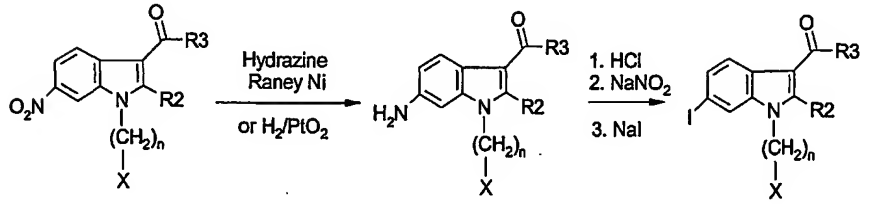
The above materials were generally prepared following Scheme 1 with the exception that N-methyl-2-piperidinemethyl chloride is used in place of acetoxylalkylhalides for the alkylation of the indole 1-position.

Scheme 1



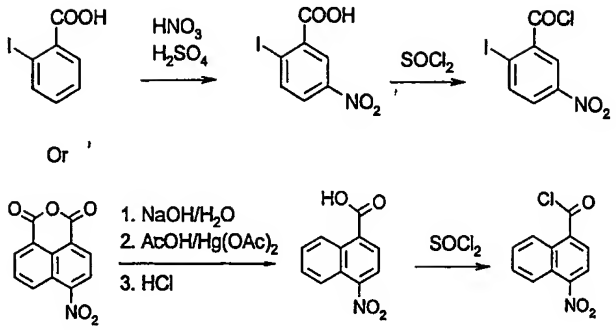

When Z = $NO_2$, the structures can be transformed to different substituents using methods outlined in Scheme 2.

Scheme 2



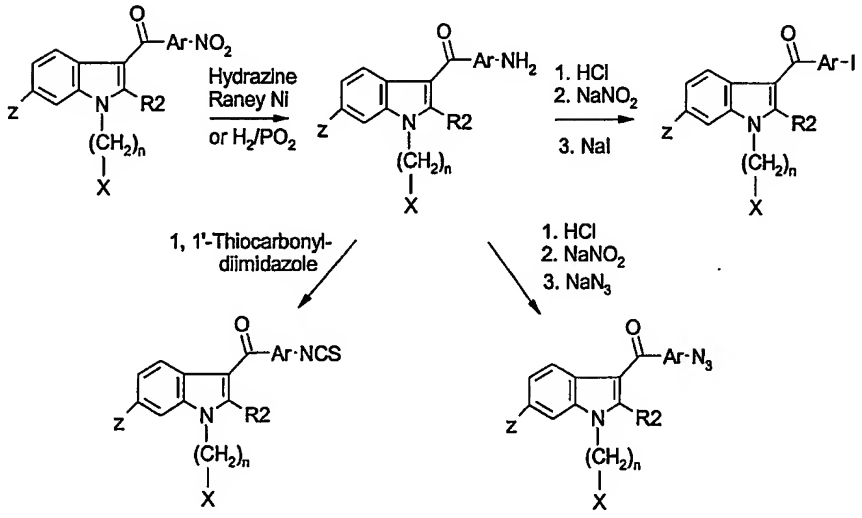

The commercially unavailable R3-COCl used in Scheme 1 can be prepared according to Scheme 3.

Scheme 3




After these acid chlorides are connected at the indole 3-position, the nitro group therein can be further transformed into amino, iodo, azido, and isothiocyanate groups according to the methods outlined in Scheme 4.

Scheme 4




Examples of specific analogs were prepared as follows:

**1-(N-Methyl-2-piperidinyl)methyl-3-(3-quinolinecarbonyl)-1H-indole.**

To the suspension of 200 mg (1.5 mmol) of anhydrous $AlCl_3$ in 8 ml absolute methylene chloride was added 287.4 mg (1.5 mmol) 3-quinolinecarbonyl chloride in 5 ml methylene chloride and the reaction mixture was stirred 30 min at room 22-

25 °C. The (N-Methyl-2-piperidinyl)methyl-1H-indole 228.3 mg (1.0 mmol) in 5 ml of methylene chloride was added by dropwise during 1.5 h and the mixture stirred 36 h. The reaction was work-up by addition of 20 ml 2M solution of sodium hydroxide and extracted by ethyl acetate (3x20 ml). The combined extract dried by sodium sulfate. After removing of solvents the rest (0.365 g) was purified by chromatography (silica gel, toluene-triethylamine, 10:1).

**1-(N-Methyl-2-piperidinyl)methyl-3-(1-adamantanecarbonyl)-1H-indole.**

To the stirring solution of the diethyl aluminum chloride (1.5 ml 1 M soln. in hexane, 180.8 mg, 1.5 mmol) in 10 ml absolute methylene chloride was added at room temp. 298.0 mg (1.5 mmol) 1-adamantanecarbonyl chloride in 5 ml of methylene chloride and the reaction mixture was stirred 15 min. The solution of (N-Methyl-2-piperidinyl)methyl-1H-indole (228.3 mg, 1.0 mmol) in 5 ml of methylene chloride was added during 3 min and mixture was stirred and reflux 48 h. The reaction was work-up by addition of 20 ml 2M solution of sodium hydroxide and extracted by ethyl acetate (3x20 ml), washed to times by water and two times by brine.. The combined extract dried by the mixture of sodium sulfate and potassium carbonate. After removing of solvents the rest was purified by chromatography (silica gel, methanol ethyl acetate 1:1).

**1-(N-Methyl-2-piperidinyl)methyl-3-(2-iodo-5-cyano)benzoyl-1H-indole.**

1-(N-Methyl-2-piperidinyl)methyl-3-(2-iodo-5-amino)benzoyl-1H-indole (111.6 mg, 0.236 mmol) was dissolved in 3 ml of water containing 43 mg (1.179 mmol) of hydrogen chloride (101 mkl 38% HCl in 3 ml $H_2O$). The this solution was added at stirring sodium nitrite 16.64 mg (0.241 mmol) in 1 ml of water at 0 °C. After 1 h the obtained diazonium salt was gradually added to solution of cuprous cyanide (23.5 mg, 0.264 mmol) in sodium cyanide (28.25 mg (0.528 mmol) in 1 ml of water at 60 °C. The reaction mixture was diluted by water, extracted ethyl acetate (3x15 ml), dried sodium sulfate and after removing of solvent purified by chromatography (silica gel, methanol-ethyl acetate, 1:2).

A person of ordinary skill in the art, understanding the disclosures for the

general preparation and specific preparation examples would know how to modify the disclosed procedures to achieve the above listed analogs.

The prepared cannabinoid compounds were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity for the CB2 receptor). As used herein, "binding affinity" is represented by the $IC_{50}$ value which is the concentration of an analog required to occupy the 50% of the total number (Bmax) of the receptors. The lower the $IC_{50}$ value, the higher the binding affinity. As used herein a compound is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a compound that has an $IC_{50}$ of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor. The binding affinities ($K_i$) are expressed in nanomoles (nM).

For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al; A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al; Determination and Characterization of a Cannabinoid Receptor in a Rat Brain, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al; "5'-azido $^{8}$-THC: A Novel Photoaffinity Label for the Cannabinoid Receptor", J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80 °C, were thawed on ice. To the stirred suspension was added three volumes of TME (25mM Tris-HCl buffer, 5 mM $MgCl_2$ and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4 °C for 30 min. At the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 µg of membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine serum albumin (BSA), 0.8 nM [$^{3}$H] CP-55,940, and various concentrations of test materials at 30 °C for 1 hour. The samples were immediately filtered using a

Packard Filtermate 196 and Whatman GF/C filterplates and washed with wash buffer (TME) containing 0.5% BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations was normalized between 100% and 0% specific binding for [$^3$H] CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield $IC_{50}$ values. Data from at least two independent experiments performed in duplicate was used to calculate $IC_{50}$ values which were converted to $K_i$ values using the using the assumptions of Cheng et al; "Relationship Between the Inhibition Constant ($K_i$) and the concentration of Inhibitor which causes 50% Inhibition ($IC_{50}$) of an Enzymatic Reaction", Biochem. Pharmacol., 22, 3099-3102, (1973), which is incorporated by reference herein.

For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P.R. Dodd et al; "A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures", Brain Res., 226, 107 - 118 (1981) which is incorporated by reference herein. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption. The CB2 binding assay was conducted in the same manner as the CB1 binding assay. The binding affinities ($K_i$) were also expressed in nanomoles (nM). The structures, binding affinities and selectivities are summarized in Table 1.

As can be seen from the results in TABLES 1 and 2, some of the compounds, for example, 2-7, show a high selectivity for the CB2 receptor. The inventive compounds described herein have high potential when administered in therapeutically effective amounts for providing a physiological effect useful to treat a variety of disease conditions. Naturally, the invention also encompasses any physiologically acceptable salts, diasteromers, enantiomers, double bond isomers and mixtures of the above inventive compounds.

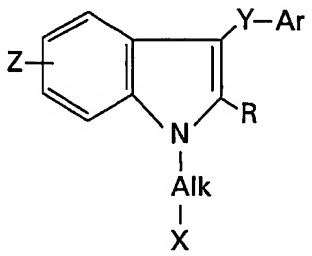
In addition, some of the iodide and fluoride containing compounds, for example, 2-7 or 2-24, are potential radioactive probes which would be useful for

imaging *in vivo* the distribution of cannabinoid receptors. Further, azido containing compounds would be useful as affinity probes for characterizing binding pockets of cannabinoid receptors.

While preferred embodiments of the foregoing invention have been set forth for purposes of illustration, the foregoing description should not be deemed a limitation of the invention herein. Accordingly, various modifications, adaptations and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention.

**What Is Claimed Is:**

1. A compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers, or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of

any of the above.

2. The compound of claim 1, wherein:

Z comprises hydrogen;

Alk comprises a $C_{1-2}$alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen;

Y comprises carbonyl; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

3. The compound of claim 1, wherein:

Z is H;

R is H; and

Ar is 2-iodo-5-nitrophenyl.

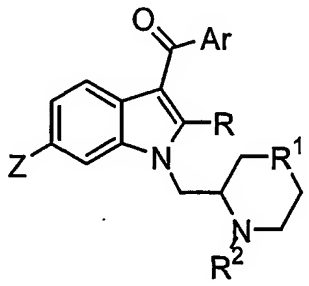
4. The compound of claim 1, wherein:

Z is H;

R is H; and

Ar is 2-iodophenyl.

5. A compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers, or mixtures thereof:



wherein:

Z comprises hydrogen;

R comprises hydrogen;

$R^1$ comprises N, O, S or $CH_2$;

$R^2$ comprises $CH_3$, $CF_3$, $CH_2C{\equiv}CH$, $CH_2CH{=}CH_2$ or $CH_2Ph$; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

6. The compound of claim 5, wherein:

Z is H;

R is H;

$R^1$ is $CH_3$;

$R^2$ is H; and

Ar is 2-iodo-5-phenyl.

7. The compound of claim 5, wherein:

Z is H;

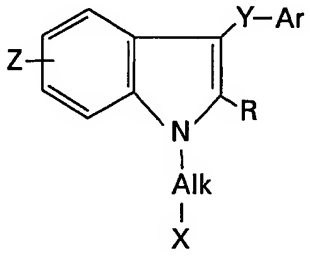
R is H;

$R^1$ is $CH_3$;

$R^2$ is H; and

Ar is 2-iodophenyl.

8. A pharmaceutical preparation comprising a therapeutically effective amount of a compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

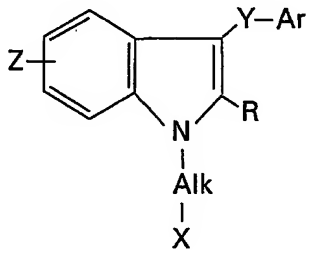
R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl;

pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

9. A method of stimulating a cannabinoid receptor in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

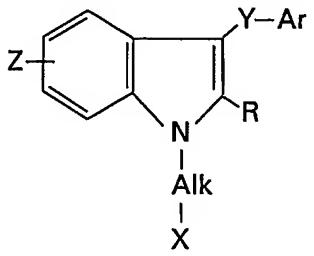
X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

10. A method of selectively stimulating a CB2 cannabinoid receptor in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected

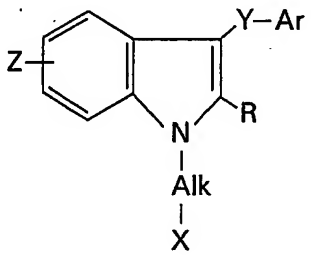
from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

11. A method of providing a physiological effect in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound of Formula I below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one

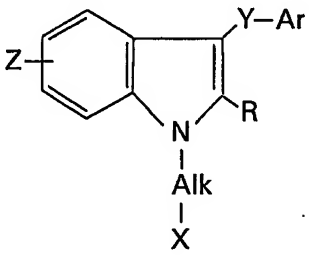
heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

12. A method of treating a condition in an animal or individual comprising administering to the individual or animal in need of such treatment an amount of a compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

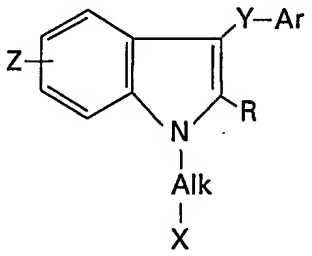
X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.

13. A method of providing a physiological effect in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound of the formula below, including physiologically acceptable salts, diasteromers, enantiomers, double bond isomers or mixtures thereof:




wherein:

Z comprises at least one substituent independently chosen from hydrogen; halogen; hydroxy; alkoxy; thioalkoxy; aryl and lower alkyl;

Alk comprises an alkyl group or a substituted alkyl group;

X comprises a 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a substituted 5, 6 or 7 member heterocyclic ring, including at least one heteroatom independently selected from oxygen, nitrogen and sulfur; a bicyclic ring; or a bicyclic ring including at least one heteroatom independently selected from oxygen, nitrogen and sulfur;

R comprises hydrogen, CN, CHO, an alkyl group or a substituted alkyl group;

Y comprises carbonyl, CH=CH (cis or trans), CONH or C=NH; and

Ar comprises adamantyl; azoadamantyl; phenyl; napthyl; 9-anthracenyl; pyridinyl; quinolinyl; isoquinolinyl; quinazolinyl; an aliphatic bicyclic ring; an azabicyclic ring; a heterobicyclic ring; any of the above with no more than two substituents each independently selected from amino, halogen, hydroxy, nitro, nitroso, azido, isothiocyanato, cyano, COOH, $CONR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl or substituted alkyl, $NCOR^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl, $CF_3$, $NSO_2R^3R^4$ where $R^3$ and $R^4$ each independently comprise H, alkyl, substituted alkyl or $CF_3$; or a salt of any of the above.